Remarks

As a preliminary comment, please note the Request for Continued Examination (RCE) and the Petition for Extension (two months) submitted together with this response.

As a further preliminary matter, it is noted that the declaration under 37 CFR 1.131 of Douglas A. Lorenz is also enclosed as part of this response.

The specification has been amended at page 3, line 20 by deletion of the phrase "now U.S. Patent No. _____,", in order to obviate the objection raised by the Examiner.

Claims 1-15, 18-44, 47-72, 75-92, 95-102, 104-112, 115-122, 124-132, and 135-163 are pending.

Claims 16-17. 45-46, 73-74, 93-94, 103, 113-114, 123, and 133-134 were previously canceled.

Claims 3-11, 19-24, 32-40, 48-53, 60-68, 76-81, 88-91, 96-101, 108-111, 116-121, 128-131, 136-141 and 148-150 have been withdrawn from consideration due to the election-of-species requirement set forth in the Office Action mailed on April 11, 2003.

Claims 1-2, 12-15, 18, 25-31, 41-44, 47, 54-59, 69-72, 75, 82-87, 92, 95, 102, 104-107, 112, 115, 122, 124-127, 132, 135, 142-147, and 151-163 are currently under examination.

It is noted that claim 95 was listed on the Continuation Sheet as pending, but its disposition as withdrawn, rejected or allowed was not otherwise indicated. It is respectfully believed that the Examiner intended claim 95 to be listed as rejected, and Applicants have so treated the claim for purposes of this response.

Independent claims 1, 30, 58, 86, 106, and 126 have each been currently amended to state that in Applicant's compositions, the drug and the (concentration-enhancing) polymer are combined as a simple physical mixture, as supported at page 11, lines 2-5. The significance of this amendment is discussed below.

The Objection To The Specification

The objection to the specification has been obviated by deleting the phrase "now U.S. Patent No. _____,". Applicants reserve the right to re-insert the complete phrase when a U. S. patent corresponding to WO 99/01120 issues.

The §112 Rejection

Claims 146 and 155 continue to be rejected under 35 U.S.C. §112, second paragraph, the Examiner having stated that "...it is not clear how the aqueous solution is formed in a use environment such as in vitro and in vivo."

Applicants traverse the rejection on the basis that it is untenable in law and in fact. Applicants note that the rejected claims are composition claims and that, as such, it matters not how the "solution" is made or formed. The point that matters is whether one skilled in the art would understand what a "solution" is, i.e., whether the claims would be clear and understandable. Definiteness under §112 is essentially a requirement for precision and definiteness of claim language. If the scope of subject matter embraced by a claim is clear, and if an Applicant has not otherwise indicated that he intends that claim to be of a different scope, then the claim does particularly point out and distinctly claim the subject matter which the Applicant regards as his invention." In Re Borkowski, 164 U.S.P.Q. 642, at 645-646 (C.C.P.A. 1970). §112, second paragraph thus calls for precision and definiteness, meaning that one skilled in the art must be able to tell with a reasonable degree of certainty whether his or her conduct is within or outside the scope of the claim. In the instant application, those skilled in the art well know what a "solution" is, such that claims 146 and 155 are clear and understandable. The Examiner has provided no factual basis supporting why the term "solution" would not be clear and understandable. The Examiner has provided no legal basis why the manner of making a solution is important to a composition claim. Applicants respectfully submit they are in compliance with 35 U.S.C. §112, second paragraph, and respectfully request withdrawal of the rejection.

The rejection over Okada

Per paragraphs 4 and 5 of the Office Action, claims 1-2, 12-15, 18, 25-31, 41-44, 47, 54-59, 69-72, 75, 82-87, 92, 95, 102, 104-07, 112, 115, 122, 124-127, 132, 135 and 142-145 continue to be rejected under 35 U.S.C. 102(b) as being anticipated by Okada et al. (US 5,496,561). The Examiner stated, in pertinent part:

> Applicants argue that Okada does not disclose a "composition comprising a drug in a solubility-improved form and a cellulosic polymer" and does not disclose "a polymer that is member of the group required by all of Applicants'

claims." Applicants state that Okada discloses corn starch use in the composition and does not disclose drugs other that the free form of the drugs as described in example 7 and 9. Applicants concluded by stating that because Okada does not disclose a composition comprising a solubility-improved form of a drug and one of the cellulosic ionizable polymers required by applicants, Okada does not disclose the elements of Applicants' claims and Okada thus not therefore anticipate the claims and the rejection should be withdrawn.

5. Applicants' arguments filed 05/19/04 have been fully considered but they are not persuasive.

To begin with, the rejection is maintained as described in the previous office action. A solubility-improved form is according to applicants' specification is that the term "solubility-improved form" as employed herein refers to a form of the drug, which has increased solubility relative to the least soluble form of the drug known. Thus, the term implies that a less soluble form of the drug exists and is either known or has been determined, i.e., known, for example, from the scientific or patent literature, or determined by or otherwise known to the investigator. A "solubility-improved form" may consist of a highly soluble form of the drug alone, may be a composition comprising a highly soluble form of the drug plus inert excipients, or may be a composition comprising the drug in a poorly or highly soluble form and one or more excipients which have the effect of increasing the solubility of the drug, regardless of the length of time for which the solubility is increased. Examples of "solubility-improved forms" include but are not limited to: (1) a crystalline highly soluble form of the drug such as a salt; (2) a high-energy crystalline form of the drug; (3) a hydrate or solvate crystalline form of a drug; (4) an amorphous form of a drug (for a drug that may exist as either amorphous or crystalline); (5) a mixture of the drug (amorphous or crystalline) and a solubilizing agent; or (6) a solution of the drug dissolved in an aqeuous or organic liquid." "Alternatively, the term "solubility-improved form" refers to a form of the drug alone or in a composition as is described above that, when delivered to an in vivo environment of use (such as, for example, the gastrointestinal tract of a mammal) or a physiologically relevant in vitro solution (such as phosphate buffered saline or a Model Fasted Duodenal solution described below) provides, or is capable of providing, at least temporarily, a concentration of drug that is at least 1.25-fold the equilibrium concentration of drug in the use environment. (As used here, the term "equilibrium concentration" is defined below.)" "A solubility-improved form of a drug is one that meets at least one of the above definitions."

Applicants in the remarks confirmed that at least example 7 discloses a salt of a drug and the salt of a drug is more soluble that the basic drug and that form of a drug will read on the solubility-improved form. Okada discloses pharmaceutical composition comprising crystalline form of a drug (column 3, line 32); polymer such as hydroxypropylmethylcellulose acetate succinate, hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate and carboxymethylethyl cellulose (column 3, lines 36-39, column 4, lines 20-25); plasticizers such as triethyl citrate, triacetin, polyethylene glycol, castor oil, polysorbitan monooleate, glycerine fatty acid ester (column 5, lines 5-8); hydroxypropylmethylcellulose acetate succinate, hydroxyproylmethylcellulose phthalate, and cellulose acetate phthalate are some of the polymers now recited by amendment in claim 1. Therefore, Okada discloses some of the polymers recited in the amended claims and thus meets that limitation. Okada discloses every limitation of the designated claims.

> Okada administers the composition comprising active agent and polymers such as hydroxypropylmethylcellulose acetate succinate, hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate and carboxymethylethyl cellulose (column 3, lines 36-39, column 4, lines 20-25 column 5, lines 55-61). Administration at essentially the same time reads on administering the drug and the polymer at the same time. Essentially the same time is essentially at the same time. [Pages 4-5 of the Office Action]

Applicants continue to traverse the rejection based, *inter alia*, on the grounds previously advanced, and Applicants' remarks from their previous responses are incorporated by reference in this regard.

Applicants traverse the rejection, particularly in light of the claims as now amended. Before discussing the traversal, Applicants emphatically note their disagreement with the Examiner's position that Okada constituted an anticipation of Applicants' claims prior to the instant amendment. There is no composition specifically disclosed or enabled in Okada that combines a drug in a solubility-improved form with a cellulosic ionizable polymer. The fact that some of the individual elements (e.g., drugs generally and some of Applicants' polymers) disclosed randomly in Okada might be appropriately combined with the aid of Applicants' own disclosure is insufficient to support the rejection because there is no written description or enablement in Okada of Applicants' invention. It is clear that Okada never, by way of description or example, specifically disclosed any formulation comprising a solubility-improved form of a drug and a cellulosic ionizable concentration-enhancing polymer. An enabling disclosure is not 'tossing out the mere germ of an idea' but the provision of 'reasonable detail...in order to enable members of the public to understand and carry out the invention'. Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366 (Fed. Cir.) *cert denied* 118 S. Ct. 397 (1997). Similarly, in respect of the instant rejection Okada never provides any description of Applicants' invention.

In addition, the current amendments to the claims even more clearly distinguish Applicants' invention from Okada. Specifically, all independent claims rejected over Okada now require that the drug and polymer are combined as a simple physical mixture, an element not disclosed by Okada. The features attributed by the Examiner to Okada, particularly the cellulosic polymers mentioned at page 5, lines 7-9 of the Office Action, are disclosed as coatings (column 3, line 37) and membranes (column 4, line 12). But, coatings and membranes are not physical mixtures with the

drug they may surround; rather they are distinct and different from a composition in which the drug and concentration-enhancing polymer are combined as a physical mixture.

There can be no doubt that the drug/polymer physical mixtures required by Applicants are distinct from, hence not anticipated by, anything disclosed in Okada. That is because Applicants themselves discuss embodiments in which the drug and polymer are in physical contact without being physically mixed. More specifically, Applicants state, at page 10, line 23 to page 11, line 6, that:

> The solid compositions of the present invention are generally combinations comprising the solubility-improved form and concentration-enhancing polymer. "Combination" as used herein means that the solubility-improved form and concentration-enhancing polymer may be in physical contact with each other or in close proximity but without the necessity of being physically mixed. For example, the solid composition may be in the form of a multi-layer tablet, as known in the art, wherein one or more layers comprises the solubility-improved form and one or more different layers comprises the concentration-enhancing polymer. Yet another example may constitute a coated tablet wherein either the solubility-improved form of the drug or the concentration-enhancing polymer or both may be present in the tablet core and the coating may comprise the solubility-improved form or the concentration-enhancing polymer or both. Alternatively, the combination can be in the form of a simple dry physical mixture wherein both the solubility-improved form and concentration-enhancing polymer are mixed in particulate form and wherein...

The definitional text quoted above unquestionably differentiates Applicants' physical mixtures from the drug/polymer combinations alluded to in Okada. Okada discloses only embodiments in which drug and polymer are not mixed. The skilled art worker, having read Applicants' specification and being aware of the definitions employed therein, would readily realize that Okada does not disclose a drug/polymer physical mixture, but rather only controlled release dosage forms containing a drug and polymer as unmixed components, i.e., a drug and a polymer membrane or coating, wherein the drug and polymer are merely in close proximity.

The Examiner is also reminded that Applicants' claims explicitly require that the maximum drug concentration (claim 1), the area under the AUC curve (claim 30), or the relative bioavailability (claim 58) be enhanced over that for a control composition not containing polymer. That requires that the concentration-enhancing polymer dissolve along with the drug so that it can inhibit precipitation of dissolved drug (page

14, lines 24-27). Such a composition is, on its face, completely distinct from Okada. The stated purpose of Okada is to make a controlled release dosage form by forming a rate-limiting membrane around a central core. Such a membrane performs its function of controlling release by remaining intact, not by dissolving as implicitily required in Applicants' invention. A physical mixture of drug and polymer, which functioned by dissolving (as it must in order to enhance concentration) would defeat the purpose of Okada's invention. Clearly, Okada provides no basis for anticipation.

The Rejections Over Curatolo and Patel

Claims 1, 30, 58, 106, 126, 146, and 155-163 stand rejected as anticipated under 35 USC 102(e) by Curatolo et al. (US 6,548,555) and by Patel (US 2003/0215496).

The rejection over both references is obviated by the submission herewith of the Rule 131 Declaration of Douglas A. Lorenz. The Lorenz declaration, together with the laboratory notebook pages appended thereto, establishes completion of Applicants' invention prior to February 9, 1999, the earliest effective date of Curatolo et al. By establishing that the invention was made prior to Curatolo, Applicants have also established that it was made prior to November 23, 1999, the earliest effective date for Patel, US 2003/0215496. Thus, both documents are removed as references, and it is accordingly respectfully requested that the §102(e) rejection over each reference be withdrawn.

In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

Respectfully submitted,

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